Case study. Neonatal Vaccination Against RSV: An Industry Perspective

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The RSV Illness burden in infants

- **The incidence of RSV hospitalizations in children has been increasing 4% annually from 1993 to 2000**
- **RSV is associated with ~1.9 million physician visits, ~378,000 ER visits and ~227,000 hospital outpatient visits per year RSV causes ~86,000 hospitalizations in US children <5 years annually**
- **59% of all RSV hospitalizations occur in infants < 6 months old; (38% of hospitalizations occur in infants < 2 months old)**
- **RSV causes more than 10% of all hospitalizations in infants 3-11 months**

adapted from HICUP, NAMCS, NHAMCS data

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Possible approaches to RSV vaccine development

Approach	Advantages	Disadvantages
Subunit, purified protein, fusion protein	Minimal reactogenicity issues for parenteral administration	Risk of exaggerated illness with wt RSV; immune response low
DNA	Probable minimal reactogenicity/adverse event issues	Immune response in animals poorly predictive of human response
Vector	High CTL and humoral target expression potential	Immune response, protection uncertain; safety in newborn
Live attenuated virus	Proven approach for mucosal and parenteral administration; high CTL and humoral target expression	Biologically plausible reactogenicity/adverse event profile; transmission issues
Mucosal delivery	Target local immunity	Adjuvant reactogenicity, safety

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Clinical Challenges for Development of a Neonatal Live Respiratory Virus Vaccine

- **Selection of a candidate vaccine**
- **Establishment of an immune correlate of protection**
- **Determination of efficacy**
- **Acceptable reactogenicity**
- **Determination of frequency and consequences of transmission**
- **Acceptable safety profile for rare adverse events**
- **Evaluation of a combination vaccine product**

Some or all of these challenges apply to other RSV or respiratory vaccine candidates

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Strain selection
Immune correlates
Efficacy

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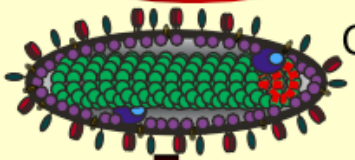
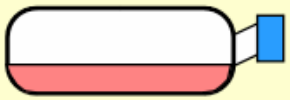
RSV Evaluation of Live Respiratory Syncytial Virus Vaccine Candidates



Candidate vaccine virus

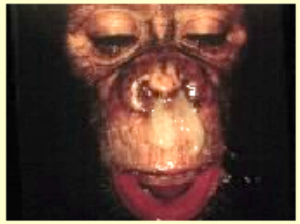


analyze phenotype

Mice

Cotton rats

Juvenile chimpanzees



Adults

Sero (+) older children

Sero (-) 6 month olds

Final Goal

Sero (-) 1 month olds

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RSV rRSV Vaccine Trials in Seronegative Children

	Virus (10^5 pfu)	% Infected	Virus Replication	Neut. Ab Response %	Vaccine-Associated Illness
6-24 mo	cpts248/404	87	4.2 (0.4-5.6)	68	wheezing (1)
6-24 mo	rA2cp248/404ΔSH	100	4.3 (1.9-5.5)	86	none
6-24 mo	rA2cp248/404/1030ΔSH	100	2.7 (1.2-3.5)	86	none
6-24 mo	rA2cp248/404ΔNS2	50	2.3 (0.3-4.2)	40	none
6-24 mo	rA2cp530/1009ΔNS2	14	1.5 (1.0-2.0)	7	none
1-2 mo	cpts248/404	76	4.0 (1.6-5.1)	0	congestion (77%)
1-2 mo	rA2cp248/404/1030ΔSH	94	3.5 (1.6-4.3)	19	none

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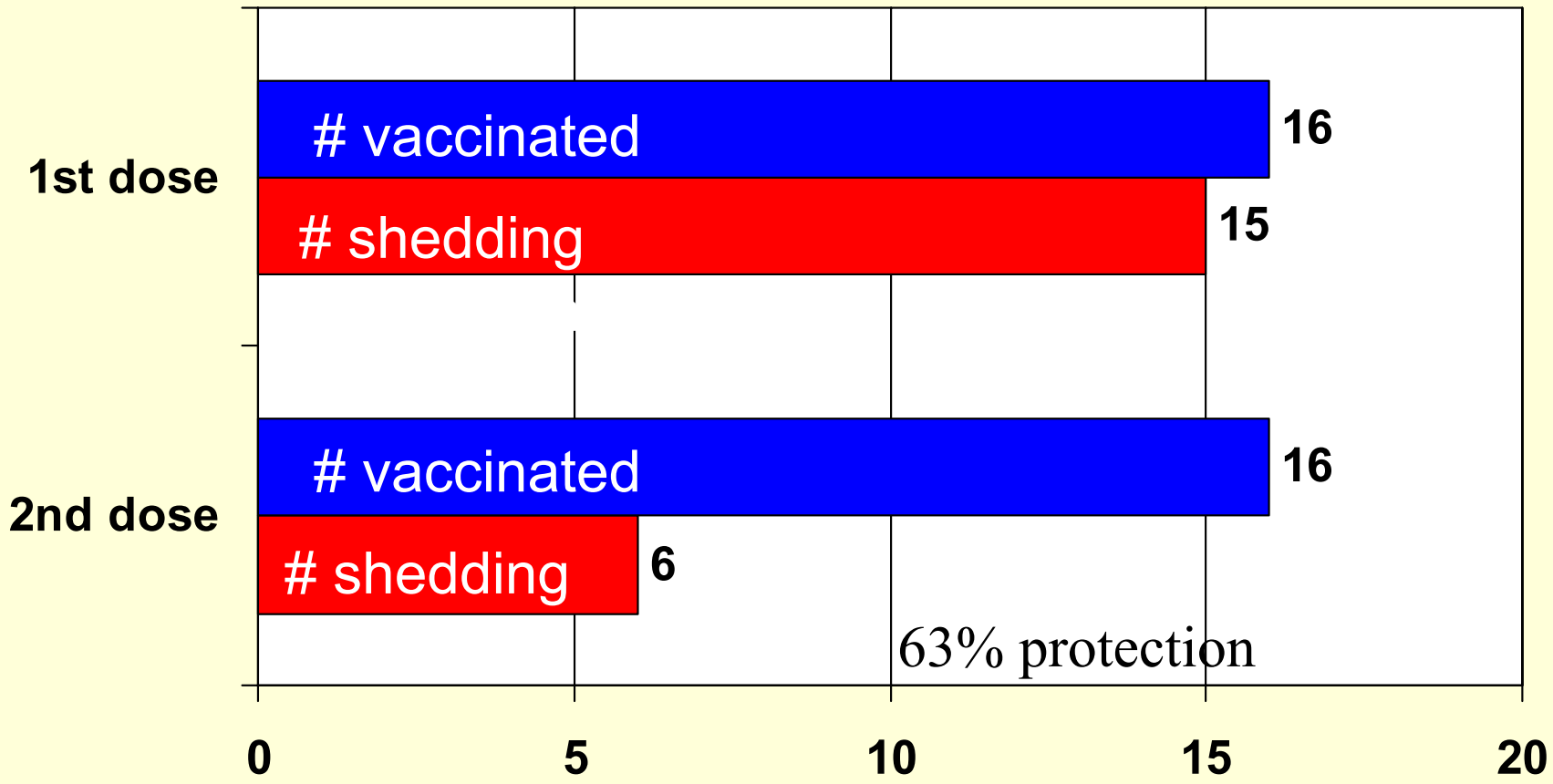
Indirect evidence of efficacy with the more attenuated rA2248/404/1030/ΔSH delivered at $10^{5.3}$ log10 pfu to infants 4-12 weeks of age



Karron et al, 2003 RSV Symposium, Nov 2003, Stone Mountain, GA

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Efficacy against RSV LRI can be determined in a relatively small population of subjects…..

Table 5. Sample Sizes Needed for Vaccine Trials Using Respiratory Syncytial Virus Lower Respiratory Infection as the Endpoint

Vaccine Efficacy, %	Children 0-12 mo				Children 0-24 mo,	
	Power of 0.8		Power of 0.9		Power of 0.8	
	n/Group	Total n	n/Group	Total n	n/Group	Total n
40	1840*	3680	2420	4840	2200	4400
50	1130	2260	1480	2960	1350	2700
60	750	1500	980	1960	900	1800
70	530	1060	680	1360	630	1260
80	380	760	490	980	460	920

* Numbers have been rounded up to even 10s.

Fisher, R et al, Pediatrics,1996

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RSV strain selection, immune correlates, and efficacy

- **Selection of a live attenuated RSV vaccine strain with desirable properties is possible**
- **A phenotypically and genotypically stable live RSV vaccine virus can be developed**
- **Immune parameters may underestimate efficacy against re-immunization and should not necessarily preclude moving forward with a candidate vaccine**
  - Consider: Use of a live attenuated RSV vaccine strain as a challenge for candidate vaccines (live, vector, subunit, DNA)
- **Efficacy against LRI can be determined in a population of less than 2000 subjects**

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Acceptable reactogenicity

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Evaluation of reactogenicity

- Relatively small studies can give an early indication about the relationship of vaccine to common symptoms
- For intranasal vaccines it is important to determine whether adventitious agents may be a contributor to symptoms

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RSV rA2cp248/404+cp45PIV3 Combination Vaccine Study: Shedding, Duration, and Mean Peak Titer

		Mean Duration of Shedding (Days)		Mean Shedding on Peak Day (pfu/ml log_{10})	
Group	Number Shedding/ Number vaccinated (%)	RSV	PIV3	RSV	PIV3
RSV	11/12 (92)	14	0	2.8	<0.5
PIV3	11/12 (92)	0	15	<0.5	3.8
RSV PIV3	19/21 (90) 16/21 (76)	15	 15	3.4	 2.1
Placebo	0/9	0	0	0	0

Belshe et al, RSV after 45 years, Segovia, Spain, 2001

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RSV/PIV3 Combination Study: Reactogenicity Data

Vaccine	No.	Temp. ≥ 38C (≥ 100.4F)	Cough	Rhinorrhea	LRI	AOM
RSV	12	2	7	11	0	4[c]
PIV3	12	1[a]	4	8	0	1[d]
RSV/PIV3	21	7[b]	7	19	0	7
Placebo	9	4	3	5	0	1

a. Shed wt RSV

b. 1 shed enterovirus

c. One each shed wt PIV, adenovirus, and influenza virus

d. Shed wt influenza

Adapted from Belshe et al, RSV after 45 years, Segovia, Spain, 2001

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Evaluation of less common biologically plausible reactogenicity

- **e.g. Wheezing-**
  - Study size is determined by the baseline incidence of wheezing in the population and the degree to which an increase in risk should be ruled out

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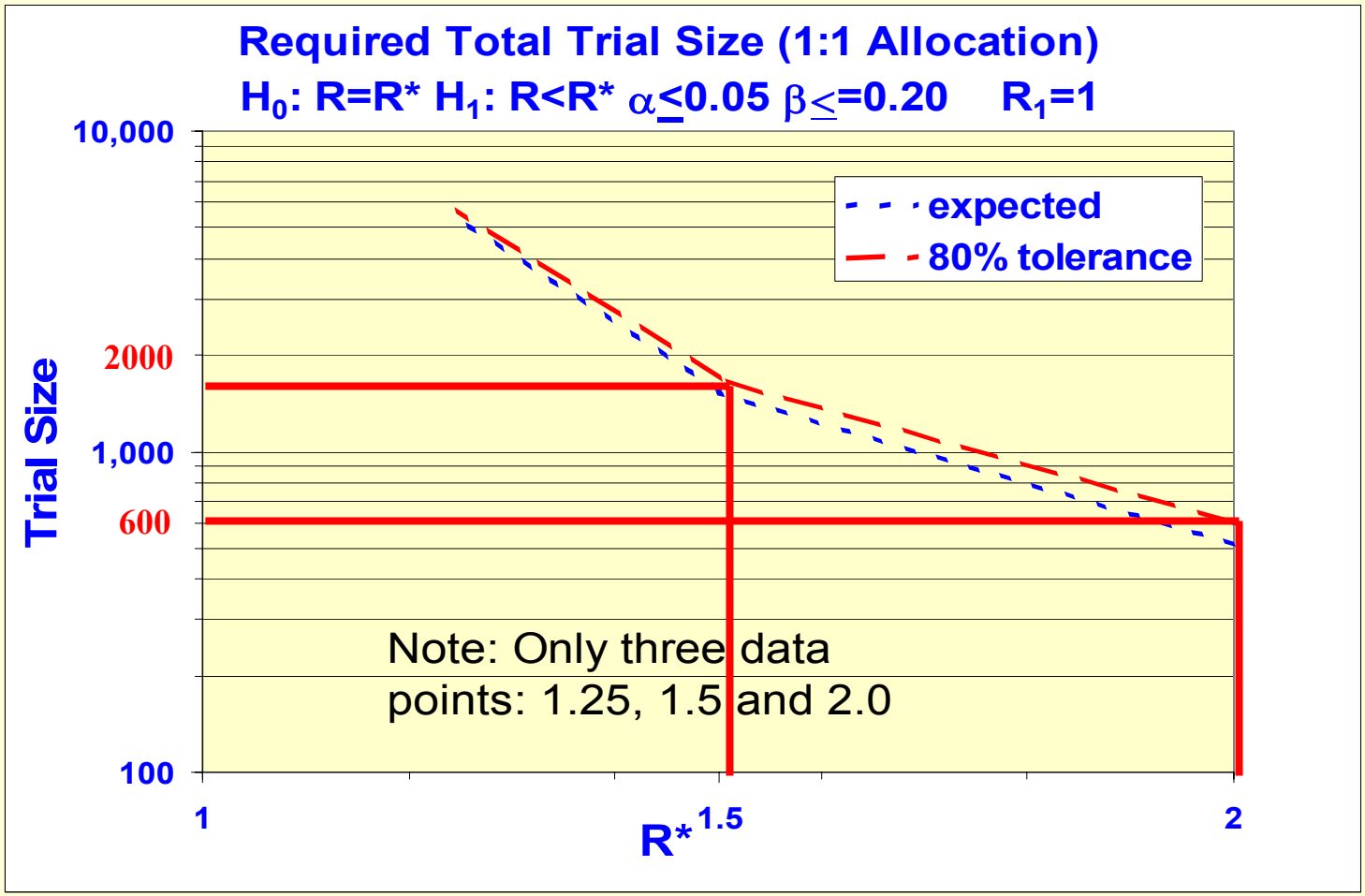
If baseline wheezing incidence is 1/10…



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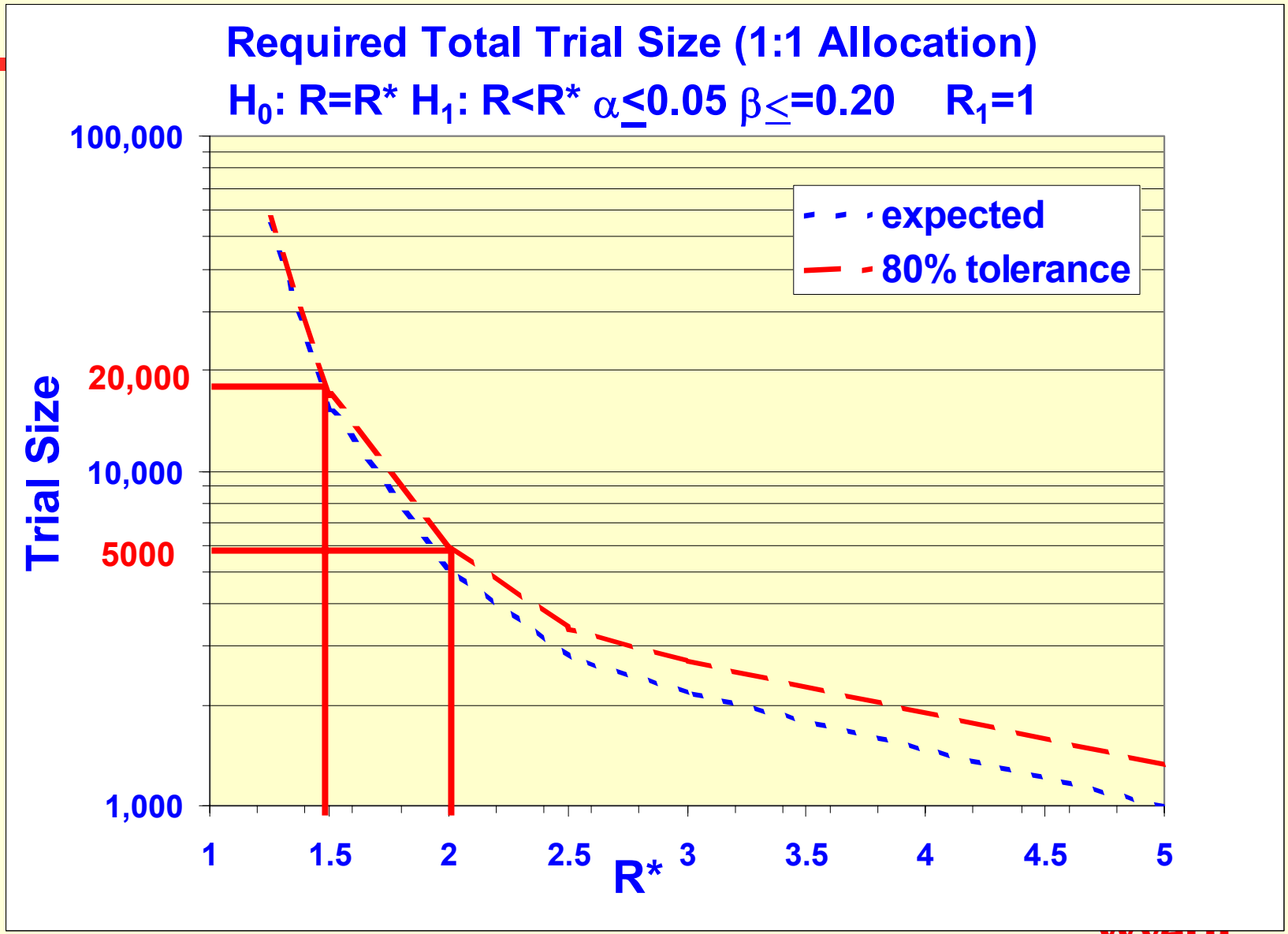
If baseline incidence of wheezing is 1/100…



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Critical questions to address *prior* to designing a trial to rule out wheezing after live (or other intranasal) neonatal RSV vaccine…

- **For what period of time does wheezing need to be evaluated after vaccine?**
- **What is the baseline rate of wheezing over the intended observation period?**
- **What level of increased relative risk for wheezing would be considered acceptable for a vaccine that is 70%, 80%, 90% efficacious against LRI?**

Government agencies, investigators, health care providers and industry need to reach consensus on an acceptable level of common biologically plausible reactogenicity events

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Determination of frequency and consequences of transmission

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Experience from a FluMist™ Daycare Transmission Trial- Conclusions

- **In the day care setting transmission rates were estimated to be 0.6% – 2.4%**
- **No phenotypic or genotypic reversion observed in shed or transmitted viruses**
- **Observed rate >10 fold lower than wild type influenza transmission rate**

Despite this study demonstrating a low rate of transmission in a setting maximizing the potential for transmission, concern about the potential for FluMist spread became a significant issue post-licensure

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Acceptable safety profile for rare serious adverse events (SAEs)

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Evaluation of uncommon biologically plausible SAEs

- **e.g. Apnea/Complications**
  - Study size is determined by the baseline incidence of the SAE in the population and the degree to which an increase in risk should be ruled out

Assume ≅1/1000 baseline incidence

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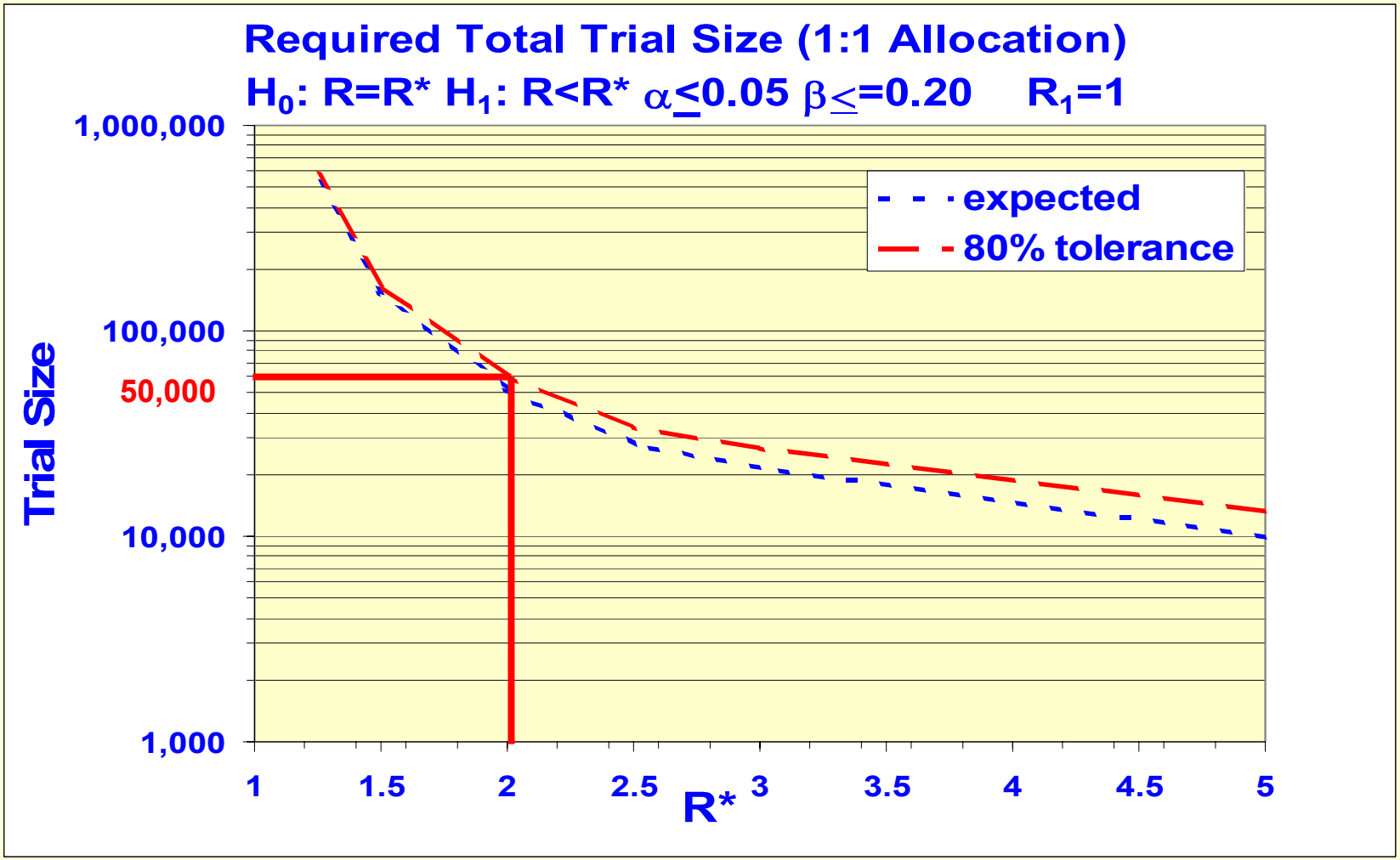
Safety: Sample Size Event Frequency 1/1000 (0.1%)



Critical questions to address *prior* to designing a trial to rule out rare SAEs after live (or other intranasal) neonatal RSV vaccine…

- **For what period of time does the SAE need to be evaluated after vaccine?**
- **What is the baseline rate of the SAE over the intended observation period?**
- **What level of increased relative risk for SAE would be considered acceptable for a vaccine that is 70%, 80%, 90% efficacious against LRI?**

Government agencies, investigators, health care providers and industry need to reach consensus on an acceptable level of rare biologically plausible SAEs

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Evaluation of a combination vaccine product

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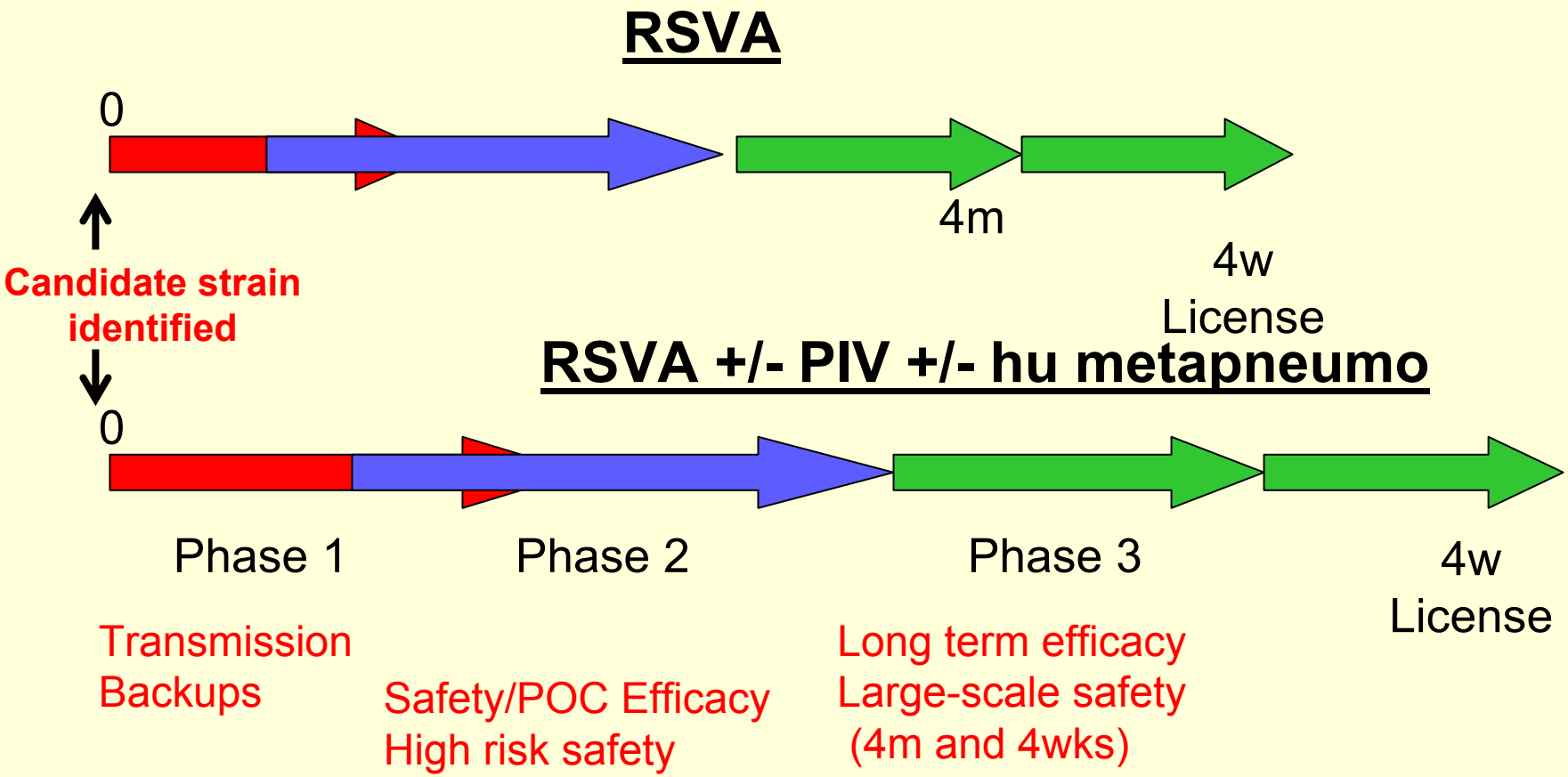
Combination vs. single agent approach…



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Case study. Neonatal Vaccination Against RSV: An Industry Perspective - Conclusions

- **Candidate selection and determination of efficacy may be relatively straightforward**

But…

- ***Early* consensus must be reached on acceptable level of common and rare biologically plausible adverse events for a given level of vaccine efficacy**
- **For live vaccine or vector, *early* consensus must be reached on acceptable level of transmission**
- **Decision on breadth of respiratory disease coverage should be balanced with timeline for development**

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"Provocative" questions for the panel:

- **Is the development of a live intranasal neonatal RSV vaccine feasible or is the live virus vaccine approach a thing of the past?**
- **What approaches remain attractive for a neonatal RSV vaccine?**

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Backup Slides

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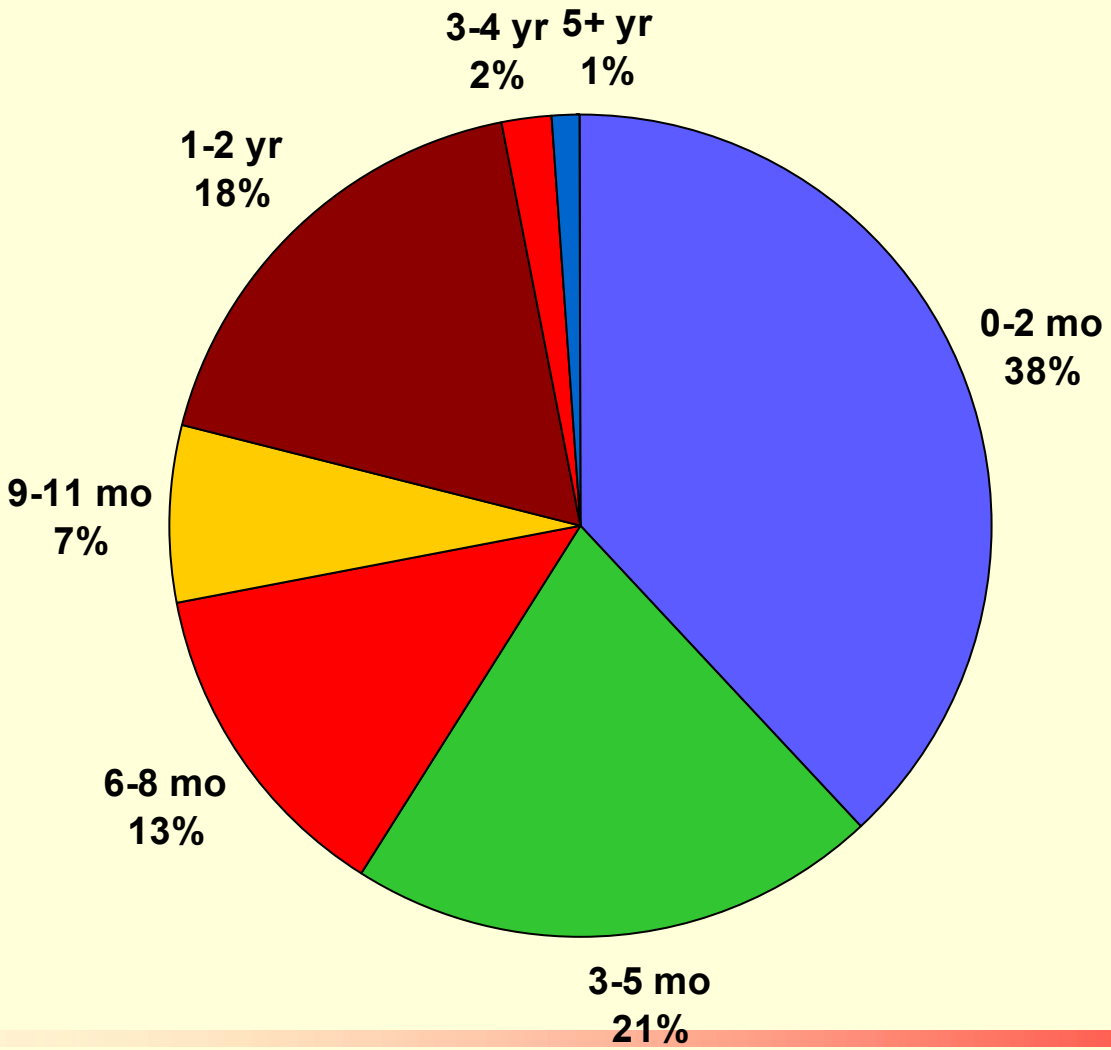
Age Distribution of RSV Hospitalizations, 2000



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National Database Analysis

- **HCUP (Healthcare Cost & Utilization Project)**
  - Hospital discharge data, 1993-2000
  - Funded by AHRQ
- **NAMCS (National Ambulatory Medical Care Survey)**
  - Physician office visit data, 1997-2000
  - Funded by CDC
- **NHAMCS (National Hospital Ambulatory Medical Care Survey)**
  - Hospital outpatient and ER visit data, 1997-2000
  - Funded by CDC

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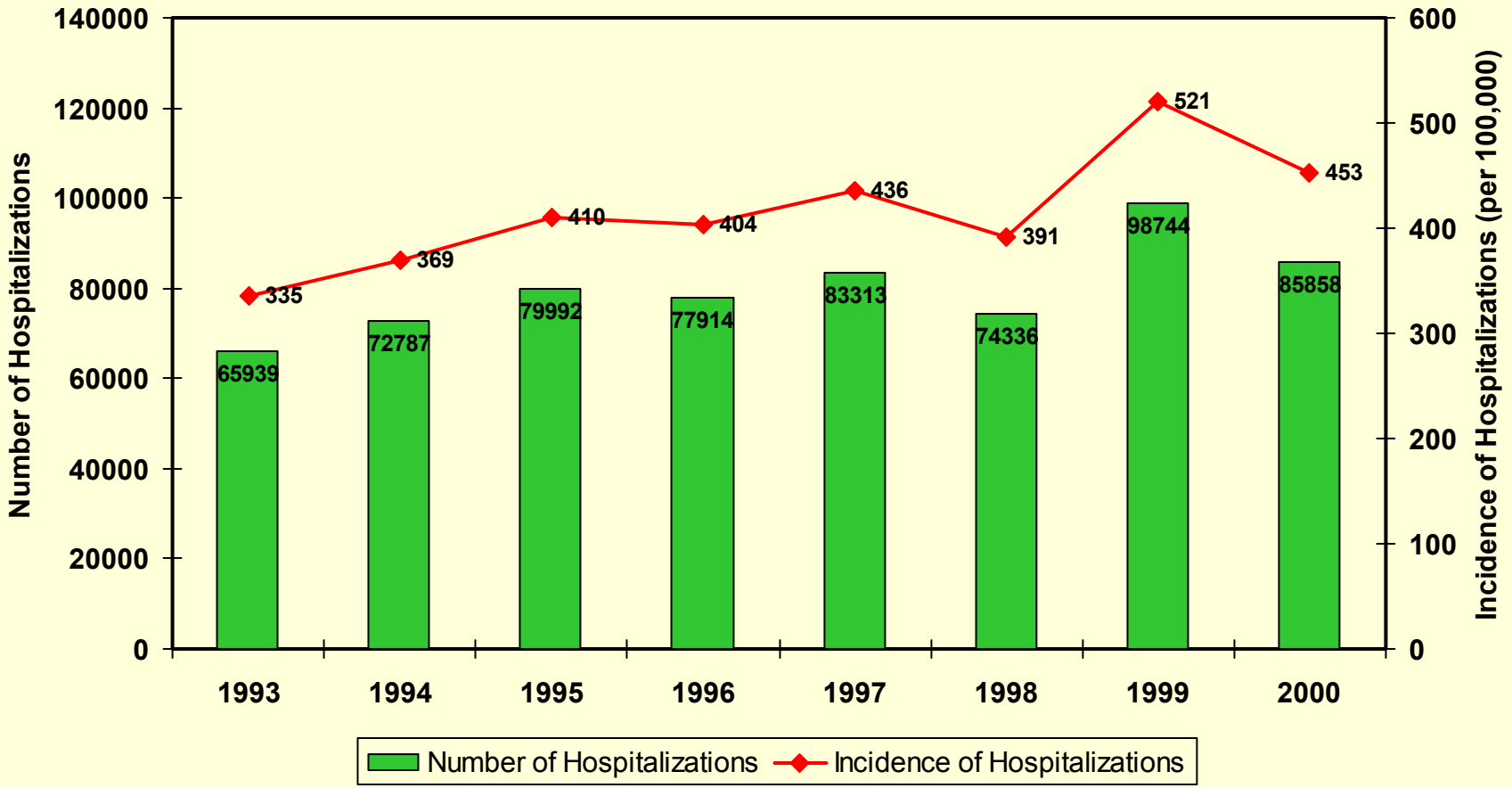
Annual Incidence of RSV Hospitalizations Among Children < 5 Years Old



Increase 4% annually, p = 0.023

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Experience from a FluMist™ Daycare Transmission Trial

- **Randomized (1:1), double-blind, placebo-controlled**
- **197 children age 8 - 36 months**
  - 98 FluMist
  - 99 placebo (93 in playgroups with vaccinees)
- **51 playgroups in two cities in Finland**
  - 45 had both vaccine and placebo children
  - 43 were in separate buildings with little chance of co-mingling outside of playgroups of participants and staff
  - Average of 4.1 study children per playgroup
  - Children attended daycare $\geq$ 3 days/week and $\geq$ 4 hours/day
  - Each placebo child exposed to 1.9 vaccinees

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Experience from a FluMist™ Daycare Transmission Trial

- **One of the largest and most comprehensive vaccine virus transmission studies**
- **Nasal cultures on the first two days after dosing and at least 3x/week for 3 weeks**
  - Over 2,000 cultures: ~10/child
  - Extensive genotyping and phenotyping
- **Designed to optimize the chance of detecting vaccine virus transmission ("worst case")**
- **Statistical methodology**
  - Estimation of probability of transmission based on Reed-Frost model

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Experience from a FluMist™ Daycare Transmission Trial-Results

- **80% of vaccine recipients shed vaccine virus**
  - 32% H1N1, 12% H3N2, 74% Type B, 6% shed all three
  - Mean days shedding = 7.6
- **Wild type A/H3N2 circulating in community**
- **7 placebo children shed any influenza virus**
  - Two shed wild type A strains
  - One shed Type B vaccine virus at day 15 visit only (Transmission Case)
  - Four shed type A virus that could not be identified as wild-type or vaccine virus

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Characteristics of a desirable candidate strain for an infant RSV vaccine

After administration to adults or seropositive children, little to no virus shedding should be documented by culture and there should be no respiratory symptoms attributable to vaccine

After administration to seronegative children 6-24 months of age, virus shedding should occur in the majority with peak mean titers < 4.0 log pfu, and minimal to no respiratory symptoms attributable to vaccine. There should be no lower respiratory tract symptoms attributable to vaccine.

After administration to seronegative infants 4-12 weeks of age, virus shedding should occur in the majority after the first dose, with peak mean titers < 4.0 log pfu and minimal to no respiratory symptoms attributable to vaccine. There should be no lower respiratory tract symptoms attributable to vaccine. Protection against shedding after a second dose of vaccine delivered 4-6wks later should be present in 50% or more of subjects.

Shed viruses should be phenotypically and genetically stable.

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Conclusions of the RSV/PIV Clinical program

- An RSV vaccine strain (rA2 248/404/1030/ΔSH) has been developed with high take rates, favorable attenuation characteristics, and efficacy against re-challenge in infants 4-12 weeks of age.
- We anticipate that genetically stable, suitably attenuated vaccine strains can be made by incorporation of stable point mutations and gene deletions. Strains incorporating these changes should be available for clinical trials in 2003-2004.
- RSV(cpts248/404) and PIV (cp45) strains have been given in combination to seronegative children 6-18 months of age with good vaccine responses, as demonstrated by virus shedding and serology.
- cp45 has demonstrated a safety profile comparable to placebo in a phase II study in children 6-18 months of age and would be a suitable strain to include in an RSV/PIV vaccine.

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